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Title Page

Safety of Natalizumab reinfusion in Multiple Sclerosis patients during active Sars-Cov2 infection

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Highlights

- NTZ infusion is safe during active Sars-CoV-2 infection.
- NTZ infusion during Sars-Cov-2 infection is not associated with delayed recovery.
- NTZ shouldn't be postponed in positive Sars-CoV-2 pwMS to limit risk of relapses.
- NTZ may prevent Sars-CoV-2 CNS invasion through integrin blockade.

Summary

COVID-19 pandemic represented a challenge in the management of treatments for Multiple Sclerosis (MS), such as Natalizumab (NTZ). NTZ interferes with the homing of lymphocytes into the central nervous system, reducing immune surveillance against opportunistic infection. Although NTZ efficacy starts to decline 8 weeks after the last infusion, increasing the risk of disease reactivation, evidence is lacking on the safety of reinfusion during active SARS-CoV-2 infection. We report clinical outcomes of 18 pwMS receiving NTZ retreatment during confirmed SARS-CoV-2 infection. No worsening of infection or recovery delay was observed. Our data supports the safety of NTZ redosing in these circumstances.

Key words: Natalizumab, Multiple Sclerosis, SARS-CoV-2, safety

Background

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is still considered a global health issue, due to its high mortality rate and morbidity burden worldwide. In the past months intense research has been dedicated to understanding whether immune depressed individuals, such as patients with multiple sclerosis (MS) treated with immunosuppressants, may have worse outcomes after COVID-19, compared to healthy subjects.

Many studies have shown that therapies for MS present an acceptable safety profile with no relevant relationship between COVID-19 severe outcomes and disease modifying therapies (DMTs) use, except for anti-CD20 therapies (Sormani et al., 2021; Zabalza et al., 2021; Salter et al., 2021). Nevertheless, the safety of treatment continuation during active infection has not been explicitly explored. This is particularly interesting for drugs with a sequestering mechanism of action, like NTZ, whose suspension is associated with the risk of a time dependent disease reactivation. Infection by SARS-CoV-2, in fact, may last longer than the estimated safety intervals of retreatment (Plavina et al., 2017) posing the question of risk/benefit of reinfusion in patients with active infection.

There is no consensus on the optimal management of NTZ in such circumstances.

This paper illustrates a case experience of 18 people with Multiple Sclerosis (pwMS), from 6 Italian MS centers, who received NTZ infusion before proving negative to SARS-CoV-2 swab.

Methods

We retrospectively collected data from 18 relapsing-remitting pwMS under NTZ treatment, infected by SARS-CoV-2 between October 2020 and May 2021, from 6 Italian MS centers (see Table 1 for demographic and clinical features of the cohort).

Patients were selected according to the following additional criteria:

1) Infection by SARS-CoV-2 between two consecutive NTZ infusions
2) Positive RT-PCR nasopharyngeal swab at the time of NTZ reinfusion
3) Consenting to be infused with NTZ before achieving negative SARS-CoV-2 swab

The following variables were collected and analyzed: baseline demographic, lifestyle, and clinical characteristics of MS (age, disease duration, median EDSS, total NTZ infusion and regimen) and outcomes of SARS-CoV-2 infection (COVID-19 symptoms at onset, at the time of and after reinfusion, date of first positive swab, date of the closest positive swab with respect to NTZ reinfusion, and date of first negative swab).

The descriptive statistical analysis was performed using SPSS program version 23.0

Results

All patients included in the study had at least one symptom of COVID-19 at onset; in particular, 72% (13/18) complained of anosmia, 66% (12/18) ageusia, 44% (8/18) fever or myalgias or headache, 38% (7/18) nasal congestion, 33% (6/18) cough and 16% (3/18) sore throat. None of them experienced gastrointestinal symptoms. All of them received NTZ infusion before achieving a negative SARS-CoV-2 molecular swab. One patient was found positive on the day of his first NTZ infusion.

At the time of NTZ reinfusion 6/18 were still symptomatic for COVID-19, while 12/18 were asymptomatic. NTZ was reinfused in a median interval of 48 (0-73) days after the pre-COVID19 infusion and specifically, those on standard interval doses (SID, n=7) were reinfused after 30 (0-36) days and those in extended interval doses (EID, n=11) after 54 days (42-73). None of the patients reported worsening of SARS-CoV-2 symptoms or developed new neurological symptoms suggestive of central nervous system (CNS) invasion by SARS-CoV-2 after redosing. Patients still symptomatic at the time of reinfusion presented a mean time to full recovery after NTZ of 10±12 days. For the whole study cohort, the mean interval from first symptoms to NTZ reinfusion was 19±9 days while the mean interval from the first COVID-19 symptom to full recovery was 13±9 days and the mean interval from first positive swab to first negative swab was 32±15 days.

Discussion

Our study highlights that NTZ redosing in pwMS during active SARS-CoV-2 infection is not associated with worsening of COVID-19 symptoms or recovery delay. NTZ is a humanized monoclonal antibody directed against alpha4-beta1 integrins expressed by circulating mononuclear cells. Through receptor binding, NTZ impairs the homing of inflammatory lymphocytes from the circulation into the CNS via the blood brain barrier (Steinman, 2014), thus reducing the inflammatory mediated damage as well as the immunosurveillance against opportunistic pathogens. In order to guarantee a receptor saturation sufficient to prevent lymphocytes migration, NTZ has to be administered every 4-6 weeks, although a partial efficacy may last up to 12 weeks (Plavina et al., 2017).

SARS-CoV-2, beyond lung infection, may involve several other organs, including the CNS. CNS invasion may occur through direct infection of the neural cells via disrupted BBE, olfactory pathway or infected immune reservoir cells (Iadecola et al., 2020).

Moreover, damage to the CNS may be also due to systemic hyperinflammatory response to SARS CoV-2 leading to a secondary cytokine release syndrome (Iadecola et al., 2020). While NTZ reinfusion might lead to new/worsened neurological complications due to the lack of immune

surveillance, treatment delay might potentiate the migration of dysregulated lymphocytes into CNS enhancing local hyperinflammation (Breton, 2010).

In this study, we selected a special cohort of patients who, in order to limit the risk of disease relapse, consented to be reinfused before achieving a negative swab.

Indeed, after NTZ therapy, no one of our patients experienced any systemic or neurological clinical worsening related to CoVID-19, suggesting that NTZ does not facilitate SARS-CoV-2 replication inside the CNS. Additionally, we did not observe any new symptoms affecting the gastrointestinal tract which is another target for both SARS-CoV-2 invasion and NTZ action.

The mean time to symptoms recovery in our cohort was in line with the outcomes observed in the general population (Rhee et al., 2021), meaning that NTZ does not reduce the viral clearance. Moreover, all of our patients had mild COVID-19, and none required oxygen support or hospitalization.

Although this study presents several limitations, the most important being the small sample size and not including severe COVID-19 patients, based on our data, we can conclude that NTZ has no detrimental effect on COVID-19. Conversely, emerging evidence supports the hypothesis that NTZ might even be beneficial in counterbalancing infection by limiting SARS-CoV-2 cells entry via integrin blockade (Aguirre et al., 2020; Sigrist et al., 2020).

In our cohort 7/18 pwMS received the infusion in line with their ordinary schedule, while the majority of them had to postpone the infusion mainly due to difficulties in accessing the MS centers. Nevertheless, our data demonstrate that NTZ reinfusion in positive patients with mild COVID-19 is reasonably safe. When circumstances allow, in order to minimize the risk of MS rebound or of possible exacerbation of the COVID-19 itself, we suggest not to delay retreatment.

Conflict of interests:

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Landi D: received travel funding from Biogen, Merck-Serono, Sanofi-Genzyme, Teva, speaking or consultations fees from Sanofi-Genzyme, Merck-Serono, Teva, Biogen, Novartis, Roche;
Cola G: nothing to disclose;
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Fantozzi R: nothing to disclose;
Centonze D: is an Advisory Board member of Almirall, Bayer Schering, Biogen, GW Pharmaceutical, Merck Serono, Novartis, Roche, Sanofi-Genzyme and Teva and received honoraria for speaking or consultation fee from Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme and Teva. He is also the principal investigator in clinical trials for Bayer Schering, Biogen, Merck Serono, Novartis, Roche, Sanofi-Genzyme;
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Table 1 Baseline demographic, clinical characteristics and COVID-19 outcomes before and after NTZ infusion of the cohort

	n=18
Age, years, mean ± SD	38,56±10,56
Female sex, n (%)	15 (83)
Smokers, n (%)	4 (22)
MS disease duration, years, mean ± SD	9,36±4,83
EDSS median, range	1 (0-5)
Total NTZ infusion, mean ± SD	46±27
Patients in SID, n (%)	7/18 (39%)
Patients in EID, n (%)	11/18 (61%)
Symptomatic for COVID-19, n	18/18
Symptomatic for COVID-19 at NTZ reinfusion , n	6/18
Previous NTZ infusion - infusion during COVID-19, days, median, range	48 (0-73)
First COVID-19 symptom - recovery, days, mean ± SD	13±9
First positive swab - first negative swab, days, mean ± SD	32±15
Worsening of COVID-19 symptoms after reinfusion, n	0/18